Mercury

CAS Registry Number 7439-97-6

I. Physical and Chemical Properties

Mercury is found in the environment in the metallic (Hg^0), inorganic (Hg_2^{+2}, Hg^{+2}), and organic (alkyl) forms.

Description	Silvery, odorless heavy liquid
Molecular formula	Hg
Molecular weight	200.59 g/mol
Air concentration conversion	Not applicable for mercury salts; 1 ppm = 8.34 mg/m^3

II. Overview

The brain and the kidneys are the primary targets of mercury toxicity with the central nervous system more sensitive than other organs. There is good evidence from human low-dose chronic exposures that fetuses exposed *in utero* are more sensitive to the toxic effects of mercury than adults. Children are potentially more susceptible than adults due to differences in the stages of brain development and organ growth that occur during the fetal, infant, and childhood developmental periods. Elemental and methylmercury readily cross the placental barrier; mercuric species, which do not readily cross the adult blood-brain barrier, are able to cross into the brain in neonatal stages due to the incompletely formed blood-brain barrier. In the brain, elemental mercury and methylmercury are slowly transformed to mercuric ion, which tends to remain at the site of formation. The toxic effects associated with exposure to elemental mercury are believed to be due to the mercuric ion.

III. Principal Sources of Exposure

The principal sources of exposure to mercury in the general population are ingestion and inhalation of mercury compounds from dental amalgams, and ingestion of fish (fresh water and marine) and seafood which contain mercury, primarily as methylmercury. Adults and children may also be exposed to small amounts of elemental mercury from broken thermometers, barometers, fluorescent lights, electric switches and inhalation of atmospheric mercury.

In the environment, mercury comes from natural and anthropogenic sources. Mercury can be released into the air through geothermal activity and the weathering of mercury ore-containing rock. Anthropogenic sources of mercury, primarily from the combustion of fossil fuels, and incineration of medical and municipal waste, contribute greater than 80% of the mercury emitted from point sources

according to the Agency for Toxic Substances Disease Registry (ATSDR, 1999) and 25% of overall (natural and anthropogenic) mercury emissions to the atmosphere (U.S. EPA, 1997). Based on the most recent inventory by the California Air Resources Board (CARB, 2000), annual statewide industrial emissions of mercury in 1998 were 9,714 lbs, and ambient air levels were 1.6 ng/m^3.

Once in the environment, interconversion between the different forms of mercury can occur. Conversion of inorganic mercury to methylmercury occurs primarily in microorganisms especially in aquatic systems. In the methylated form, mercury bioaccumulates up the food chain and can reach very high concentrations in some fish, many of which are consumed by humans.

The majority of exposure to mercury is dietary. The 50^{th} percentile of mercury ingestion for the U.S. population is 1.4 µg/day (NRC, 2000) while exposures via inhalation are on the order of 30 to 40 ng/day (1.6 ng/m^3 X 10 to 20 m^3/day), based on the average ambient concentration. The ratio of the average statewide ambient concentration to OEHHA's chronic Reference Exposure Level is 0.02. Exposures near sources of emissions may be higher.

IV. Potential for Differential Effects

There is a considerable body of evidence from human poisoning episodes that exposure *in utero* and postnatally results in developmental neurotoxicity. Thus, infants and children are susceptible subpopulations for adverse health effects from mercury exposure. These effects fall into several general categories: 1) effects on neurological status; 2) age at which developmental milestones are achieved; 3) infant and preschool development; 4) childhood development (age 6 and above); and 5) sensory or neurophysiological effects (U.S. EPA, 2000).

Whereas methylmercury and elemental mercury readily cross the blood-brain barrier and the placental barrier, the mercuric ion (Hg^{2+}) does not readily cross these barriers. However, in fetuses and neonates mercuric species concentrate more in the brain because the blood-brain barrier is incompletely formed. Methylmercury and elemental mercury are lipophilic and are distributed throughout the body. In adults mercuric species accumulate more in the kidney. However, in neonates mercuric species do not concentrate in the kidneys but are more widely distributed to other tissues (National Research Council, NRC, 2000). It is possible that the increased distribution of mercuric species to the brain in fetuses and neonates accounts for some of the sensitivity of the brain to mercury during these developmental periods. The sensitivity of the fetal brain might also be due to the high proportion of dividing cells during neuronal development in the fetal and neonatal periods. These dividing cells may be more sensitive to damaging effects of mercury-protein complexes.

In addition to prenatal and postnatal dietary exposure, neonates may receive added postnatal dietary exposure to mercuric species and methylmercury from breast milk (Drexler and Schaller, 1998; Sundberg *et al*., 1999). School children can be accidentally exposed to elemental mercury which is a

curiosity and an attractive nuisance (George *et al*., 1996; Lowry *et al*., 1999). Younger children may also be exposed when elemental mercury is spilled on floors and carpets where they are more active.

A. Summary of Key Human Studies

The effects of low-dose *in utero* exposure to mercury on neurological development in school-age children were studied by Grandjean *et al*. (1997) in 917 mother-infant pairs in the Faroe Islands. Neurobehavioral tests were administered at birth and at 1 and 7 years to follow the effects of pre- and postnatal exposure to dietary methylmercury. Families in the Faroe Islands consume a diet high in protein from fish and marine mammals (whales). Mercury in maternal hair, children's hair, and cord blood was measured. Levels of mercury in the mothers' hair and in cord blood at birth were significant predictors of neuropsychological dysfunction in the children at seven years of age. Cord blood mercury was a significant predictor of dysfunctions in several tests intended to measure domain-specific neuropsychological effects: finger tapping, preferred hand; continuous performance test; mean reaction time, WISC-R digit span; Boston Naming Test (with and without cues); and California Learning Test (short-term and long-term reproduction). Maternal hair mercury was also a predictor of deficits in several tests, but most test scores were more strongly associated with mercury levels in cord-blood. These effects were seen at mercury levels at which there were no signs of toxicity in the mothers.

In the 1950s and 60s neurological disease was noted in many people living around Minamata Bay in Japan. People of all ages were affected, but effects were most severe in infants and children. The disease was traced to methylmercury pollution in the bay that accumulated to high levels in fish (10-40 ppm). Families were chronically exposed to methylmercury because fish were a major source of dietary protein. The neurological effects in children were often not recognized until they were several months old. Children with severe clinical neurological problems were born to mothers without clinical symptoms or with less severe symptoms. The clinical effects in prenatally exposed children included microcephaly, cerebral palsy, seizures, and mental retardation (Harada, 1995). Other neurological effects of mercury poisoning in this population included paresthesia, ataxia, visual defects, dysarthria, hearing effects and death. The collection of observed effects in children and adults was called Minamata disease. Takeuchi T. (1968) described three progressive stages of neuropathology for Minamata disease for fetal, infant, and adult exposures that demonstrate differential susceptibilities. The fetal pathologies were most severe showing disorganized cell layers and misoriented cells throughout the brain. Adult pathologies were least severe and more localized. Rogan (1995) noted that some children exposed to methylmercury in Minamata suffered profound effects while there were no symptoms in their mothers. All these studies suggest that children are more sensitive to the neurodevelopmental effects of mercury than are adults.

There is also some concern that subtle neurobehavioral effects may not manifest themselves until later in life following mercury exposures. Harada (1995) divided patients with non-acute Minamata disease into three types based on the time course of the appearance of mercury poisoning symptoms: gradually progressive type, escalating progressive type and delayed onset type. An example of delayed onset includes cases of constriction of the visual field (a common symptom of Minamata disease) which started two to three years after cessation of fish consumption.

In older adults the majority of mercury in the brain is mercuric ion. It is not clear whether the mercuric ion or methylmercury is the proximate toxicant responsible for toxic effects in the brain. Adult autopsies of poisoning patients and those with Minamata disease showed an increase in mercuric ion and focal lesions in the cerebrum and cerebellum which are responsible for coordination, balance and sensations (Clarkson, 1997; Davis *et al*., 1994). Prenatal exposures produced damage throughout the brain in children with clinical symptoms very much like cerebral palsy (Harada, 1995).

Similar clinical effects were observed following mercury poisoning incidents in Iraq in 1971 and 1972 (Marsh *et al*., 1981). In Iraq, families were acutely exposed to high levels of mercury when they ate bread made from methylmercury-treated seed grain. These exposures occurred over a two to three month period and children were exposed *in utero*. Marsh *et al*. (1981; 1987) identified 84 mother infant pairs exposed to methylmercury during pregnancy. Mercury levels were determined in sucessive 1 cm segments of maternal hair and peak mercury levels were correlated with the results of neurological examinations of the children and surveys of maternal symptoms. Clinical symptoms of Minamata disease were documented; parasthesis in exposed adults and neurological deficits in children. Neurological effects in children included altered muscle tone, increased deep tendon reflexes, delays in developmental milestones (i.e., walking or talking), and seizures. Mild effects were seen in children whose mothers' peak hair mercury was 68-180 ppm while the most severe effects were seen when peak hair mercury levels were 165-320 ppm.

McKeown-Eyssen *et al*. (1983) found that abnormalities of muscle tone (increased and decreased) and decreased reflexes were significantly ($p=0.05$) associated with an index of prenatal mercury exposure in boys but not girls in a study in Quebec. There was no consistent dose-response relationship in this study.

Effects in very young children (less than 5 years) are difficult to measure reproducibly and reported effects of mercury are subject to differences in age at examination, the test used, scoring criteria and other problems. In a prospective study Kjellstrom *et al*. (1986) examined a cohort of New Zealand children for whom prenatal exposure to methylmercury was estimated based on maternal hair samples. The children of 73 women whose hair mercury levels exceeded 6 ppm (high-mercury group) were matched with reference children on the basis of maternal ethnicity and age, hospital of birth and child age. In follow-up evaluations at four years of age, 52% of the high-mercury group had abnormal or questionable scores on the Denver Developmental Screening Test (DDST) compared with 17% of the control group ($p<0.05$). However, the DDST has been criticized for being insensitive to variations within the range of normal performance and therefore not particularly useful for neurobehavioral toxicology studies (Dietrich and Bellinger, 1994).

Kjellstrom *et al*. (1989) followed a cohort of 237 children up to six years of age in New Zealand. Children were placed in a high-mercury group based on mercury in maternal hair. Multiple controls were matched to each high-mercury child and 26 psychological and scholastic tests were administered to test general intelligence, language development, fine and gross motor coordination, academic attainment, and social adjustment. In the initial analysis a significant association was found between

maternal hair mercury level and domain tests for: full-scale IQ; language development; visual-spatial skills; and gross motor skills.

Davidson *et al*. (1998) tested 711 children in the Seychelles Islands at 66 months of age using a battery of standardized neurodevelopmental tests. Mothers of these children consumed about 12 fish meals per week. Hair mercury was measured in mothers and in test children. The tests used in this study provided more global scores of neurodevelopment that integrate performance over multiple separate neuropsychological domains. Some of the tests in this study overlap those in the Faroe and New Zealand studies but were given at a slightly earlier age, 5.5 years. No adverse effects of prenatal or postnatal mercury exposure were found for the six primary domain endpoints: cognitive ability, expressive and receptive language, letter and word recognition, reading and arithmatic achievement, visual and spatial ability, and social and adaptive behavior. The only significant association ($p = 0.05$) was an apparent enhanced performance on four of these six measures among children with increased exposure to methylmercury. The battery of tests used in this study have been criticized as being less sensitive to the subtle domain specific changes found in the Faroe study. Also children in this study were tested at 5.5 years of age which is a period of rapid developmental change when test assessments are less sensitive due to individual differences in the rate of cognitive maturation (NRC, 2000).

In studies of 6-7-year-old children in a fishing village in Madeira, Murata *et al*. (1999) found that the brainstem auditory evoked potentials increased by 0.058 ± 0.048 ms ($p=0.23$) and 0.128 ± 0.058 ms ($p=0.03$) at 20 and 40 Hz, respectively, when maternal hair mercury concentrations exceeded 10 µg/g. At these maternal hair mercury levels, visual evoked potentials increased by 3.16 ± 1.57 ms ($p=0.05$) and 0.62 ± 1.55 ms ($p=0.69$) at 15 and 30 minutes of arc, respectively. Although the overall effect of these changes may be small they are consistent with mercury effects on sensory and neurological function.

B. Summary of Key Animal Studies

Animal studies support the human study observations that damage to the central nervous system and kidneys are the primary toxic effects of mercury following sub-acute and chronic exposures.

Pregnant Sprague-Dawley rats were exposed on gestation days 11-14 and 17-20 to elemental mercury vapors (1.8 mg/m^3) for one or three hours per day (Danielsson *et al*., 1993). There was no difference among treatment groups for maternal weight gain and no obvious mercury toxicity in the dams. Offspring exposed *in utero* did not differ from controls by several measures including body weight, clinical signs, pinna unfolding, righting reflex (measured daily from day 2 postpartum) and negative geotaxis (at days 7, 8 and 9). However, at 3 months of age exposed males but not females showed significant decrements in four measures of spontaneous motor activity measured on three consecutive days: locomotion, rearing, rearing time and total activity measured by the interuption of infrared light beams in two grids at different levels in an activity chamber. By 14 months, the high dose animals showed hyperactivity in these same tests. At 4 months, treated males had significantly higher latency in a maze-learning test while at 15 months there was no difference between treated and control animals in a circular swim maze test. A significant difference was seen between treated and control males at 7

months in a test of habituation to novel environments. Habituation was measured as the ratio of spontaneous motor activity during the second 30 min in a test chamber to that in the first 30 min.

In a study designed to simulate the natural course of human fetal-type Minamata disease, rat fetuses were conceived in female Wistar rats pre-exposed to low oral doses of methylmercury chloride (1, 2 or 3 mg/kg/day) for 5 or 12 days prior to mating and during gestation. The effects of mercury on the fetal brain were determined by histological examination of the brains at one time point, embryonic day 22, from at least 20 fetuses from three maternal rats of each treatment group and eight individuals from two controls. The fetuses showed varying degrees of neuronal degeneration in the brain stem, cingulate cortex, thalamus and hypothalamus (Kakita *et al*., 2000). This pattern of damage was different from that seen in rats treated with methylmercury chloride in the postnatal or adult stages. In rats treated for 10 days from postnatal day 15, widespread degeneration was found in the cerebral cortex, striatum and red nucleus, while in adults treated starting on postnatal day 60, severe lesions were seen in the cerebellum and dorsal root ganglia.

In humans rapid brain growth occurs primarily during the third trimester, whereas in rats it occurs after parturition. To model the effects of methylmercury exposure during this time of rapid neuronal development, Sakamoto *et al*. (1998) orally exposed six neonatal Wistar rats to methylmercury chloride (5 mg/kg/day) starting with postnatal day 1. Body weight was monitored daily and weight loss was observed in the treated group starting on day 26. Neuropathological effects were examined in two rats, which showed severe nervous symptoms on days 32 and 34. Histologically, widespread neuronal degeneration was observed on days 32 and 34 within the cerebral neocortex, neostriatum, red nucleus, brainstem, cerebellum and spinal sensory ganglia, compared to four control rats sacrificed on day 31. Although limited in size, this study suggests that the developing nervous system is sensitive to methylmercury.

V. Additional Information

A. Regulatory Background

Neurotoxicity is the most sensitive effect of mercury exposure. In California, the acute reference exposure level for mercury is 1.8 $\mu g/m^3$, and the chronic Reference Exposure Level is 0.09 $\mu g/m^3$ (0.01 ppb) for the critical effects: hand tremor, memory disturbances, neurobehavioral and autonomic dysfunction (OEHHA, 1999; 2000). The Environmental Protection Agency (U.S. EPA, 1997; 2000) has calculated a reference dose of 0.1 µg/kg-day. This RfD was based on the combined incidence of neurological effects (i.e., age at walking and score on a neurological examination) in children exposed *in utero* to methylmercury in the maternal diet reported by Marsh *et al*. (1987) for 81 mother-infant pairs. The RfD was derived from a benchmark dose limit on the 95% lower confidence limit on the dose at a 10% risk level using a Weibull model. This level was calculated as 11 ppm in maternal hair and 44 µg/L in maternal blood. A composite uncertainty factor of ten was applied to derive an RfD of 0.1 µg/kg-day.

VI. Conclusions

Mercury is a neurotoxic substance with substantial human evidence indicating infants and children are susceptible subpopulations for this effect. However, exposures via inhalation are relatively small in California. Thus, mercury was placed in Tier 2. If evidence becomes available that localized exposures may be significant, OEHHA may revisit listing mercury under SB 25.

VII. References

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